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Menopausal hormone therapy and the risk of esophageal and gastric cancer

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A protective effect of female sex hormones has been suggested to explain the male predominance in esophageal and gastric adenocarcinoma, but evidence is lacking. We aimed to test whether menopausal hormone therapy (MHT) decreases the risk of these tumors. For comparison, esophageal squamous cell carcinoma was also assessed. This population-based matched cohort study included all women who had ever used systemic MHT in Sweden in 2005–2012. A comparison cohort of non-users of MHT was matched to the MHT-users regarding age, parity, thrombotic events, hysterectomy, diabetes, obesity, smoking-related diseases and alcohol-related diseases. Individuals with any previous cancer were excluded. Data on MHT use, cancer, comorbidity and mortality were collected from well-established Swedish nationwide registers. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using conditional logistic regression. Different MHT regimens and age groups were compared in sub-group analyses. We identified 290,186 ever-users and 870,165 non-users of MHT. Ever-users had decreased ORs of esophageal adenocarcinoma (OR = 0.62, 95% CI 0.45–0.85, *n* = 46), gastric adenocarcinoma (OR = 0.61, 95% CI 0.50–0.74, *n* = 123) and esophageal squamous cell carcinoma (OR = 0.57, 95% CI 0.39–0.83, *n* = 33). The ORs were decreased for both estrogen-only MHT and estrogen and progestin combined MHT, and in all age groups. The lowest OR was found for esophageal adenocarcinoma in MHT-users younger than 60 years (OR = 0.20, 95% CI 0.06–0.65). Our study suggests that MHT-users are at a decreased risk of esophageal and gastric adenocarcinoma and also of esophageal squamous cell carcinoma. The mechanisms behind these associations remain to be elucidated.

Additional Supporting Information may be found in the online version of this article.

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The explanation for the intriguing male predominance in esophageal and gastric adenocarcinoma might provide important clues to the etiology of these tumors and also pave the way for research examining novel preventive and therapeutic medication.[1] The up to 9-fold higher risk of esophageal adenocarcinoma among men than in women, is not explained by the sex distribution of its main risk factors, *i.e.,* gastroesophageal reflux disease and obesity.[1–5] For gastric adenocarcinoma, the incidence is 2-fold higher in men, a difference that is also not readily explained by the major risk factors, *i.e., Helicobacter pylori* infection and tobacco smoking.[6–8] The 3-fold higher incidence of esophageal squamous cell carcinoma in men is mainly explained by the sex distribution of its main risk factors, *i.e.,* heavy use of tobacco and alcohol.[9,10] Female sex hormones may prevent esophageal and gastric adenocarcinoma.[1,6] However, studies examining various sex hormone related exposures in relation to risk of these tumors have provided conflicting results.[1,6,11] Menopausal hormone therapy (MHT), also known as hormone replacement therapy, consists of estrogen or estrogen combined with progestin. Original studies examining MHT and risk of esophageal and gastric adenocarcinoma have typically been under-powered, have mostly examined one or two cancers per study and arrived at inconsistent findings.[1,11] However, meta-analyses

What's new?

Men carry an up to 9-fold higher risk to develop esophageal adenocarcinoma than women. Here the authors used menopausal hormonal therapy as a way to assess the impact of female sex hormone exposure on esophageal and gastric cancer risk. Their data show that women who have ever used menopausal hormone therapy were protected from esophageal and gastric adenocarcinoma as well as esophageal squamous cell carcinoma regardless if estrogen only or combined estrogen and progestin therapies were used. These results underscore a protective role of female sex hormones in the development of these cancers.

comparing ever-users of MHT with non-users have shown statistically significantly decreased relative risk estimates of esophageal adenocarcinoma, gastric adenocarcinoma and also of esophageal squamous cell carcinoma.[12–14] We hypothesized that MHT decreases the risk of esophageal and gastric adenocarcinoma, but not of esophageal squamous cell carcinoma. To test this hypothesis and address the limitations of the available literature, we conducted a large and population-based study enabling a possibility of comparing the risks of all three cancers in one study.

Patients and Methods

Design

This was a population-based matched cohort study based on prospectively collected data from well-established nationwide Swedish registers, comparing the risk of esophageal and gastric cancer in all women residing in Sweden exposed to systemic MHT with that of women not exposed to MHT. Entry into the cohort was between July 1, 2005 and December 31, 2012. Follow-up for both the users and non- users was until a diagnosis of cancer, death, or December 31, 2012, whichever occurred first. The non-users of MHT were frequency-matched to the ever-users on potential confounding factors. Eligible were only women 40 years or older without any previous cancer. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (number 2014/1291–31/4).

Data sources

The Swedish Prescribed Drug Registry was used to identify all individuals receiving MHT during the study period. This register started in July 1, 2005 and collects data on all prescribed and dispensed drugs in Sweden, including the names of medications, Anatomical Therapeutic Chemical classification system (ATC) codes, and the dates that treatments were dispensed. Using the unique 10-digit personal identity number, assigned to all Swedish residents upon birth or immigration, all included women were linked to the Swedish Cancer Registry, Patient Registry and the Causes of Death Registry.[15]

The Swedish Cancer Registry contains data on all malignant tumors diagnosed in Sweden since 1958. The information includes date of diagnosis, anatomical site and histological type of each tumor. The register has 98% nationwide completeness regarding both esophageal and gastric cancer,[16,17] and the recording of all cancer sites is 96% complete.[18] This register was used to identify esophageal and gastric cancer during follow-up of the ever-users and non-users of MHT and to exclude individuals with a history of any previous cancer.

The Swedish Patient Registry contains information regarding diagnoses and surgical procedures in all in-patient care and specialist out-patient care in Sweden. The register was founded in 1964, and data regarding in-patient care and out-patient specialist care has been 100% nationwide complete since 1987 and 2001, respectively.[19] The validity of the recording of all diagnoses and gynecological surgical procedures is excellent.[19,20] The registry was used to identify comorbidities used in the matching and statistical analyses. Data regarding comorbidities were retrieved since the initiation of the Patient Registry to improve ascertainment and validity of comorbidities.

The Swedish Causes of Death Registry contains data on date of death and causes of death of all Swedish residents since 1952. The registry has an overall 100% completeness regarding date of death and 99.2% completeness for cause-specific death.[21] This register was used to assess mortality.

Exposure

The MHT-exposed cohort included all women, above 40 years of age without a history of any cancer, who were ever prescribed and dispensed systemic MHT during the study period. MHT exposure was defined according to the following ATC-codes: G03C (estrogens); G03D (progestogens, only included if prescribed in combination with estrogens); and G03F (progestogens and estrogen in combination). MHT is used for treatment of menopausal symptoms and prevention of osteoporosis and is recommended as estrogen combined with progestin in women with an intact uterus (to reduce the risk of endometrial cancer) or as estrogen alone in women who have undergone hysterectomy.[22–24] Only systemic treatments were included, *i.e.*, oral tablets, dermal patches and dermal gel.

The non-exposed comparison cohort consisted of women not receiving a prescription of MHT during the study period, older than 40 years and without a history of any cancer. The non-exposed women were selected from the nationwide chemoprevention cohort, which includes up to 95% of all women in Sweden of this age group. These participants were

frequency-matched to mimic the MHT-users on the distribution of the variables age, parity, hysterectomy, thrombotic events, diabetes, obesity, smoking-related diseases and alcohol-related diseases.

Outcomes

Esophageal cancer was identified using the International Classification of Diseases version 7 (ICD-7) anatomical codes 150 (esophagus) or 1511 (cardia) and histological codes 096 for adenocarcinoma and 146 for squamous cell carcinoma in the Cancer Register. Gastric cancer was identified using the ICD-7 anatomical codes 1510, 1518 or 1519, and the histological code 096 was used only to define adenocarcinoma.[25] Patients with unspecified histological types of cancer were excluded from the analyses.

Confounders

Ten potential confounding factors were considered. First, we included only participants without a history of any cancer (to avoid bias from detection or influence of cancer treatments). The ever-users of MHT were matched to the non-users to select a group of non-users as similar as possible to the users regarding eight *a priori* selected factors. Group-level (*i.e.*, frequency) matching was used, aiming for a 1:3 ratio with exact matching on three binary variables: parity (ever-parous or non-parous, increased life time exposure to estrogen), hysterectomy (leading to earlier contact with gynecologist, and influencing the choice of what MHT treatment to use) and thrombotic events (contraindication for MHT).[26] Nearest neighbor matching was done for another five variables: age (a risk factor for cancer, determined from exact date of birth), diabetes mellitus (a proxy for obesity), obesity (which might influence the probability of receiving MHT, and is a risk factor for the studies cancers), smoking-related diseases (a proxy for smoking, which might influence both the probability of receiving MHT and the cancer risk) and alcohol-related diseases (a proxy for high alcohol consumption, which might influence both the probability of receiving MHT and the cancer risk).[26] The used matching method aims for as close to an exact match on all the included variables to reduce baseline imbalances. Finally, after the matching procedure was completed, osteoporosis was added and adjusted for in the analysis (since this is an indication for treatment with MHT).[23] All codes defining the comorbidities are presented in the Supporting Information Table 1. If an individual lacked a certain diagnosis code, this diagnosis was interpreted as absent.

Statistical analysis

The cancer risk was assessed in a conditional logistic regression model, taking into account the clustering by the exact matching variables, as well as also adjusting for all the potential confounders. Due to the study design, follow-up time for the non-users is not calculated, nor used in the analyses. The results were presented as odds ratios (OR) with 95% confidence intervals (CI). Subgroup analyses were conducted based on the regimen of MHT (estrogen only or estrogen combined with progestin) and age groups (year of birth before 1943, 1943–1951, or in 1952 or later). The age groups were defined based on the recommended ages for MHT use, *i.e.,* recommended for women aged younger than 60 years and not recommended for women aged older than 70 years.[27] Poisson regression was conducted when comparing $\leq$12 months duration of MHT treatment with $>$12 months duration.

Results

Participants

The study included 290,186 ever-users of MHT and 870,165 matched non-users of MHT. Of the ever-users, 135,988 (46.9%) dispensed estrogen only MHT and 154,198 (53.1%) dispensed a combination of estrogen and progestin MHT. The ever-users and non-users were similar regarding the prevalence of all matching variables (Table 1). The median follow-up time among the users of MHT was 7.0 years (2540 days), and the interquartile range was 4.1–7.4 years (1487–2685 days).

Risk of esophageal adenocarcinoma

Among the ever-users of MHT, 46 (0.02%) developed esophageal adenocarcinoma, while 224 (0.03%) such cases occurred among non-users (Table 1). The adjusted OR of esophageal adenocarcinoma was 38% lower among ever-users compared to non-users (OR 0.62, 95% CI 0.45–0.85) (Table 2). Among users of estrogen only MHT, the corresponding OR was 0.57 (95% CI 0.37–0.87), while the OR among women receiving estrogen and progestin combined MHT was 0.70 (95% CI 0.45–1.09). In MHT-users younger than 60 years, the OR of esophageal adenocarcinoma was particularly decreased (OR 0.20, 95% CI 0.06–0.65), while the ORs were less decreased in MHT-users aged 60–70 years (OR 0.60, 95% CI 0.34–1.07) and those older than 70 years (OR 0.79, 95% CI 0.52–1.19) (Table 3). The statistical power was insufficient to allow analyses examining duration of MHT.

Risk of gastric adenocarcinoma

There were 123 (0.04%) new cases of gastric adeoncarcinoma among the ever-users of MHT and 608 (0.07%) cases among the non-users (Table 1). Comparing ever-users with non-users, the overall adjusted OR of gastric adenocarcinoma was 0.61 (95% CI 0.50–0.74) (Table 2). Ever-users of estrogen only MHT (OR 0.60, 95% CI 0.47–0.76) and of estrogen and progestin combined MHT (OR 0.64, 95% CI 0.48–0.87) had decreased ORs of similar strength. The OR of gastric adenocarcinoma was particularly decreased in MHT-users younger than 60 years (OR 0.39, 95% CI 0.21–0.71) and less so in those of 60–70 years of age (OR 0.69, 95% CI 0.48–0.98) and in MHT-users older than 70 years (OR 0.63, 95% CI 0.49–0.81) (Table 3). When comparing $\leq$12 months duration of

Table 1. Characteristics of ever-users and non-users of menopausal hormone therapy (MHT)

	Ever-users of MHT Number (%)	Non-users of MHT Number (%)
Total	290,186 (100.0)	870,165 (100.0)
Age (in years)		
<60	108,631 (37.4)	325,747 (37.4)
60–69	93,490 (32.2)	267,323 (30.8)
≥70	88,065 (30.4)	277,095 (31.8)
Follow-up (years)		
Median (Interquartile range)	7.0 (4.1–7.4)	N/A
Parity		
Ever-parous	117,861 (40.6)	353,282 (40.6)
Comorbidity		
Hysterectomy	51,811 (17.9)	155,138 (17.8)
Thrombotic events	40,316 (13.9)	120,931 (13.9)
Diabetes mellitus	15,936 (5.5)	48,422 (5.6)
Obesity	5,146 (1.8)	15,526 (1.8)
Smoking-related diseases	13,601 (4.7)	40,994 (4.7)
Alcohol-related diseases	7,293 (2.5)	21,455 (2.5)
Osteoporosis	8,256 (2.9)	22,764 (2.6)
Esophageal or gastric cancer during follow-up		
Esophageal adenocarcinoma	46 (0.02)	224 (0.03)
Esophageal squamous cell carcinoma	33 (0.01)	174 (0.02)
Gastric adenocarcinoma	123 (0.04)	608 (0.07)

MHT with >12 months the incidence rate ratio was 0.92 (95% CI 0.43–1.97).

Risk of esophageal squamous cell carcinoma

Among the ever-users of MHT, 33 (0.01%) developed esophageal squamous cell carcinoma, while 174 (0.02%) of the non-users developed this cancer. The overall adjusted OR of esophageal squamous cell carcinoma was 43% decreased among ever-users (OR 0.57, 95% CI 0.39–0.83) (Table 2). The OR among women receiving estrogen only MHT was 0.71 (95% CI 0.46–1.09) and 0.38 (95% CI 0.19–0.75) among women receiving estrogen and progestin combined (Table 2). The OR was 0.80 (95% CI 0.26–2.44) in MHT-users younger than 60 years, 0.41 (95% CI 0.20–0.82) in users aged 60–70 years and 0.65 (95% CI 0.40–1.05) in MHT-users older than 70 years (Table 3). Comparing duration ≤12 months with >12 months, of MHT treatment rendered an incidence rate ratio of 0.45 (95% CI 0.11–1.79).

Discussion

In this study, ever-users of MHT were at a decreased risk of esophageal adenocarcinoma, gastric adenocarcinoma and esophageal squamous cell carcinoma. The estrogen only MHT-users had a decreased risk of esophageal and gastric adenocarcinoma in particular, while women using combined therapy with estrogen and progestin may be at a particularly decreased risk of esophageal squamous cell carcinoma. For esophageal and gastric adenocarcinoma, a strongly decreased risk following MHT use was found among younger women.

Strengths of this study include the complete nationwide coverage with a large sample size, the completeness of the follow-up, and the validity of the data contained in the Swedish registers used. The linkage of data between registers using the personal identity numbers available in all Swedish residents was a prerequisite for this study.[15] The Prescribed Drug Registry contains all prescribed and dispensed medications in Sweden, thus minimizing the risk of selection bias. The completeness and accuracy of the data in the Cancer Registry guarantees a robust assessment of the study outcomes.[16–18] There are, however, also limitations of the study. Confounding is a threat to observational studies in general. We could not take into account potential influence of breastfeeding and other reproductive factors, including age at menopause or number of pregnancies and deliveries, factors that may affect the lifetime cumulative estrogen exposure. There is also a possibility that women using MHT differ from women not having such treatment in terms of lifestyle factors that in turn affect the risk of the studied cancers. However, the study controlled for 10 potential confounders which should have counteracted confounding, which creates a

Table 2. The risk of esophageal and gastric cancers following ever use of different regimens of menopausal hormone therapy (MHT) compared to non-users, expressed as odds ratios (OR) with 95% confidence intervals (CI)

	Non-users Number=870,165	Ever-users Number=290,186		Estrogen only users Number=135,988		Estrogen + progestin users Number=154,198	
	Number (%)	Number (%)	OR (95% CI)1	Number (%)	OR (95% CI)1	Number (%)	OR (95% CI)1
Esophageal adenocarcinoma	224 (0.03)	46 (0.02)	0.62 (0.45–0.85)	24 (0.02)	0.57 (0.37–0.87)	22 (0.01)	0.70 (0.45–1.09)
Gastric adenocarcinoma	608 (0.07)	123 (0.04)	0.61 (0.50–0.74)	75 (0.06)	0.60 (0.47–0.76)	48 (0.03)	0.64 (0.48–0.87)
Esophageal squamous cell carcinoma	174 (0.02)	33 (0.01)	0.57 (0.39–0.83)	24 (0.02)	0.71 (0.46–1.09)	9 (0.01)	0.38 (0.19–0.75)

*Adjusted for age, parity, hysterectomy, thrombotic events, diabetes mellitus, obesity, smoking-related diseases, alcohol-related diseases, and osteoporosis (all but osteoporosis were used for matching).

comparison group as similar as possible to the exposed group at baseline. The matching on key factors mimics a randomization on the selected factors. Since some of the confounding factors were recorded to only a limited degree in the registers, *e.g.*, obesity and diabetes, the matching strategy is ideal. No validation study of obesity diagnosis in the Swedish Patient Registry has been conducted till today, although obesity is believed to be substantially underreported. The coding for diabetes mellitus (type 1 and 2) in the Swedish Patient Registry has been found to have high validity in previous studies.[20] Smoking and alcohol consumption were assessed indirectly, based on smoking-related diseases and alcohol-related diseases. Although this does not represent the true incidence of smoking and excessive alcohol consumption, it should detect the most severe and long-term consumers. We did not adjust for gastroesophageal reflux disease or *Helicobacter pylori,* the risk factors for esophageal adenocarcinoma and gastric adenocarcinoma, respectively.[1,7] However, estrogen therapy is rather associated with an increased risk of reflux and could therefore not explain the negative association between MHT and esophageal adenocarcinoma.[28] MHT use is unlikely to be associated with *Helicobacter pylori* and thus should not act as a confounder.[29] A weakness was the lack of starting dates of MHT use for women enrolled in the cohort in July 2005 (start of the study), which prohibited an assessment of duration of MHT use in relation to cancer risk. The lack of information on MHT use before 2005 resulted in a possibility that women might have received MHT before the initiation of the study, which could lead to women using MHT before the initiation of the registration were included in the non-exposed cohort. However, such exposure misclassification is likely to be at random and would thus dilute the ORs rather than explaining the decreased ORs. Further, due to the current design and statistical analyses a sensitivity analysis is not possible since no proxy date of entry is assigned to the non-users, meaning that only cases among users can be excluded from the first year of inclusion in the study. Finally, a longer follow-up than about 8 years would have been preferable when studying cancer risk. Yet the study is the largest cohort investigating the association between MHT and risk of esophageal and gastric cancer.

Table 3. The risk of esophageal and gastric cancers in ever-users of menopausal hormone therapy (MHT) compared to non-users, categorized by age group and expressed as odds ratios (OR) with 95% confidence intervals (CI)

	Ever-users Number (%)	Non-users Number (%)	OR (95% CI)[1]
Esophageal adenocarcinoma			
<60 years	3 (0.00)	43 (0.01)	0.20 (0.06–0.65)
60–69 years	14 (0.01)	67 (0.03)	0.60 (0.34–1.07)
≥70 years	29 (0.03)	14 (0.00)	0.79 (0.52–1.19)
Gastric adenocarcinoma			
<60 years	12 (0.01)	89 (0.03)	0.39 (0.21–0.71)
60–69 years	37 (0.04)	153 (0.06)	0.69 (0.48–0.98)
≥70 years	74 (0.08)	366 (0.13)	0.63 (0.49–0.81)
Esophageal squamous cell carcinoma			
<60 years	4 (0.00)	14 (0.00)	0.80 (0.26–2.44)
60-69 years	9 (0.00)	63 (0.02)	0.41 (0.20–0.82)
≥70 years	20 (0.02)	97 (0.04)	0.65 (0.40–1.05)

[1]Adjusted for age, parity, hysterectomy, thrombotic events, diabetes mellitus, obesity, smoking-related diseases, alcohol-related diseases and osteoporosis (all but osteoporosis were used for matching.

The study hypothesis was based on the unexplained strong male predominance in esophageal adenocarcinoma and moderate male predominance in gastric adenocarcinoma, which we thought would be reflected in a reduced risk among MHT-users. We thought the already explained male predominance in esophageal squamous cell carcinoma, would transfer into no association with MHT use. We cannot entirely exclude that the reduction in the risk of all three cancers may indicate healthy users bias, a sampling bias where patients receiving MHT might differ from the comparison population, mainly differences in lifestyle behavior. This could among other things be in relation to smoking and alcohol consumption, where there might be differences between different age groups, which could reflect in the different ORs

for different age groups in relation to MHT prescription. The lack of any increased risk of gastric adenocarcinoma or esophageal squamous cell carcinoma with longer duration of MHT argues in favor of non-hormonal influence. However, the matching on many health-related factors intended to counteract such bias, and the results of this study are well in line with all three meta-analyses on the topic. These meta-analyses have found decreased risk estimates of esophageal adenocarcinoma (odds ratio 0.75, 95% CI 0.58–0.98, 5 studies included),[12] gastric adenocarcinoma (risk ratio 0.77, 95% CI 0.64–0.92, 7 studies included),[13] and esophageal squamous cell carcinoma (risk ratio 0.68, 95% CI 0.48–0.96, 4 studies included).[14] Moreover, presence of estrogen receptors have repeatedly been found in both esophageal and gastric adenocarcinoma cells, and treatment with ligands binding to selective estrogen receptors could inhibit cell growth and induce apoptosis in esophageal adenocarcinoma.[30–37] It has also been suggested that sex hormones inhibit cell growth in gastric adenocarcinoma and esophageal squamous cell carcinoma.[38–40]

Progesterone receptors have been found in gastric adenocarcinoma in some studies but to a similar extent as in normal mucosa.[33,41–43] Androgen receptors have been identified in esophageal adenocarcinoma and esophageal squamous cell carcinoma, while these receptors have been inconsistently found in gastric adenocarcinoma.[43–45] Thus, sex hormonal influence might play a key role in explaining the findings of this study.

There is a need for more large-scale studies with long follow-up and adjustment for lifestyle factors before a causal relation between sex hormonal therapy and cancer prevention can be established. If the findings of the current study are supported by such research, they would encourage research examining new prevention strategies using sex hormonal therapy in high-risk individuals of esophageal or gastric cancers and of hormonal adjuvant therapy of these tumors.

In conclusion, this large population-based cohort study with robust assessments of exposures and outcomes and adjustment for several potential confounding factors found that ever-users of MHT are at a decreased risk of esophageal adenocarcinoma, gastric adenocarcinoma and esophageal squamous cell carcinoma. These findings might potentially be explained by sex hormonal effects, but this remains uncertain, and more research is required to examine the mechanisms behind these associations.

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